Remarks

Claims 18, 21-26, 30, 31, and 33-47 were pending in the subject application. By this Amendment, new claims 48 and 49 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Claims 40-43 remain pending but withdrawn from consideration. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 18, 21-26, 30, 31, and 33-49 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

The applicants acknowledge that claims 40-43 have been withdrawn from further consideration as being drawn to a non-elected invention. However, the applicants wish to reserve the right to request rejoinder of the non-elected process claims upon an indication of an allowable product claim (cell culture claim) in accordance with MPEP §821.04.

By this Amendment, claims 48 and 49 have been added. Support for claims 48 and 49 can be found, for example, at page 15, line 22; and page 20, lines 2-26 (Example 2), of the specification as filed.

Claims 18, 22-26, and 33 remain rejected under 35 U.S.C. §102(a) as being anticipated by Andrews *et al.* (Poster presentation from Cell Culture and Engineering Conference in Snowmass, CO; 2002). The applicants respectfully traverse. The Declaration under 37 C.F.R. §1.132 by Dr. Caviedes, which was submitted with the applicants' Amendment of January 27, 2006, is sufficient to show that the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application.

At page 3, the Office Action acknowledges that the Declaration is sufficient to remove P. Venegas from consideration as "another" for purposes of 35 U.S.C. §102(a). As indicated by Dr. Caviedes in the Declaration, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera also contributed to the claimed invention, but were not included as co-authors of the Andrews *et al.*

presentation because they were not directly responsible for the generation of data contained within the presentation.

The information contained in the Andrews *et al.* presentation represents preliminary work in which the objective was to determine conditions in which cells could be more efficiently cultured in order to obtain large masses of cells in reduced spaces or volumes, with contemplated applications including the extraction of cell products (*e.g.*, neurotrophic factors) and cell transplantation. The contributions of Dr. Freeman, Mr. Arriagada, and Mr. Salazar Rivera were not limited to transplantation methods ("as part of a therapy"); they also contributed to the creation of the cell culture currently claimed.

Dr. Freeman determined the size and geometry of neuronal cell aggregates conducive to cell transplantation (*e.g.*, small clusters of cells to facilitate harvesting and transplant with minimal trauma to the cells), and the culture time and conditions necessary to obtain them. For example, at least some of Dr. Freeman's contributions are embraced by claims 34, 35, and 38. Dr. Freeman was not included as a co-author of the Andrews *et al.* presentation because he participated in the research carried out subsequent to the experiments described in the presentation. Christian Arriagada and Julio Salazar Rivera contributed to the conception of the claimed invention. Mr. Arriagada and Mr. Salazar Rivera designed and carried out morphological experiments to determine when cells in the center of the cell aggregates started to become necrotic (degenerate). In addition, Mr. Salazar Rivera carried out initial transplant studies in Parkinsonian rats. For example, at least some of Mr. Arriagada's and Mr. Salazar Rivera's contributions are embraced by claims 35, 48, and 49. Mr. Arriagada and Mr. Salazar Rivera were not included as co-authors of the Andrews *et al.* presentation because they participated in the research carried out after the experiments described in the Andrews *et al.* presentation.

The subject matter pertaining to the claimed invention that is described within the Andrews *et al.* presentation was invented by Pablo Caviedes, Raul Caviedes, Juan A. Asenjo, Barbara A. Andrews, and Dario Sepulveda. Therefore, the Andrews *et al.* presentation represents the inventors' own disclosure published less than one year prior to the effective filing date of the subject application. As explained above, Thomas B. Freeman, Christian Arriagada, and Julio Salazar Rivera also contributed to the claimed invention, but were not included as co-authors of the Andrews *et al.*

presentation because they were not directly responsible for the generation of data contained within the presentation.

"[O]ne's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar." *In re Facius,* 161 USPQ 294, 301 (CCPA 1969); and MPEP §715.01(c). Therefore, under the authority of *In re Facius*, the disclosure contained in the Andrews *et al.* presentation cannot be used as a prior art reference against the applicants' claimed invention. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(a) is respectfully requested.

Claims 18, 21-26, 30, 31, 34-39, and 44-47 have been rejected under 35 U.S.C. §103(a) as being obvious over Takazawa *et al.* (U.S. Patent No. 5,219,752) in view of Studer *et al.* (International Published Application No. WO 00/05343) and further in view of Boss *et al.* (U.S. Patent No. 5,411,883). The applicants respectfully traverse.

The cell culture of the invention would not have been obvious to a person of ordinary skill in the art at the time the invention was made, based on the references cited in the Office Action. Submitted with the applicants' Amendment dated October 4, 2006 was a Declaration under 37 C.F.R. §1.132 by Dr. Pablo Caviedes, including Exhibits A-C.

The teachings of the cited references do not provide one of ordinary skill in the art with a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in independent claims 18 and 39. Only the subject application teaches a cell culture of neuronal cells of the CNS as recited in claim 18. The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as currently recited in the claims.

Claims 18 and 39 of the subject application recite that the cell culture comprises process-forming neuronal cells of the central nervous system and has a calcium concentration of 100 μM or less. The empirical data in columns 17-22 of the Takizawa *et al.* patent indicate that the aggregation of fetal kidney cells essentially occurs when a threshold calcium concentration is reached. In contrast, the inventors of the subject invention have found that process-forming neuronal cells of the central nervous system will aggregate when cultured at a calcium concentration of 100 μM or less.

The Takazawa *et al.* patent proposes that various adherent animal cells can be cultured using the method disclosed therein, including the 500-plus cells tabulated in columns 5-12. These cells represent a very diverse variety of tissues, *e.g.*, bat lung cells, goldfish fin cells, goose sternum cells, human bone marrow cells, human breast cells, human pancreatic cells, mosquito larval cells, moth ovarian cells, snail embryonic cells, viper spleen cells, *etc.* However, the only cells described in the Takazawa *et al.* patent as actually being cultured with the disclosed method are kidney cells, *i.e.*, 293 cells (human fetal kidney) and BHK 229 cells (hamster kidney). In the Declaration submitted on October 4, 2006, Dr. Caviedes indicates:

> absent supporting empirical data, such as that provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claims 18 and 39.

Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The Takazawa *et al.* patent only provides a reasonable expectation of success in culturing kidney cells as described, not neuronal cells, and certainly not neuronal cells of the central nervous system that cluster into aggregates, as recited in the claims of the subject application.

The only cells described as actually being cultured with the disclosed method are kidney cells. A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). As pointed out by the Examiner at page 5 of the Office Action, in a more recent publication, Grinstaff *et al.* report that human fibroblasts and umbilical vein endothelial cells lose their morphology and adhere to untreated polystyrene plates. In view of this "negative teaching", absent supporting empirical data, as provided in the subject application, one of ordinary skill in the art would not have a reasonable expectation of success in creating a cell culture comprising neuronal cells of the CNS that cluster into aggregates, as recited in claims 18 and 39 of the subject application.

At page 4, the Office Action states that "when considering the factors relating to determination of non-enablement, if all the other factors point towards enablement, then the absence or low number of working examples will not by itself render the invention non-enabled." However,

the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness, including a reasonable expectation of success (MPEP section 2142), *i.e.*, reasoning and/or evidence showing why one of ordinary skill in the art would reasonably extrapolate the working example with kidney cells across the entire scope of cells, or at least the process-forming neuronal cells of the CNS currently recited in the claims of the subject application. If the Examiner does not establish a *prima facie* case, the applicants are under no obligation to submit evidence of non-obviousness.

The Examiner's comments at page 5 of the initial Office Action on the merits dated September 27, 2005 seem equally relevant and applicable in considering the references cited by the Examiner here.

> While a single, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the negative teachings of the art and the lack of description and guidance present in the application, provides additional weight to the to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success of creating a cell culture comprising any type of process-forming cells .... (emphasis added)

Furthermore, assuming *arguendo* that the references cited in the Office Action support a reasonable expectation of success in producing the cell culture of the invention, the results obtained using neuronal cells of the cell culture of the invention were significantly better than could have been expected, as shown by Exhibits B and C, which accompanied Dr. Caviedes' Declaration. The experimental results in Exhibits B and C provide a valid comparison for purposes of establishing unexpected results.

As indicated in Example 1, at page 18, lines 27-30, and page 19, lines 1-5, of the subject application, and page 3 of Exhibit B (Materials and Methods—Cell Culture), the RCSN-3 cell line was initially established from a primary culture of the striatum of Fisher 344 rats, and exposed to media conditioned with the UCHT1 cell line (Caviedes R. and Stanbury J.B., *Endocrinology*, 1976, 99:549-554, which is of record). RCSN-3 cells retain the morphology of the neuronal phenotype (Cardenas A.M. *et al.*, *Neuroreport*, 1999, 10(2):363-369, which is of record). Exhibit C shows results from implantation of cells from the same RCSN-3 cell line following culture in the cell culture of the invention. Thus, the RCSN-3 cell line was originally exposed to conditioned media

from the UCHT1 cell line; cells of the cell line were subsequently used in the experiments in Exhibits B and C (and Examples 1 and 2 of the subject application). The cells of Exhibit B were not cultured in the cell culture of the invention. The cells of Exhibit C and Examples 1 and 2 of the application were cultured in the cell culture of the invention.

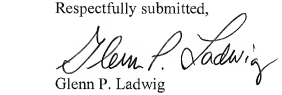
Gradual behavioral recovery (reduction of apomorphine-induced rotation scores) was observed in transplanted animals. As shown in Figure 6 of Exhibit B, rats implanted with conventionally cultured RCSN-3 cells showed a steady decrease in rotations, leveling off at 75% of the initial rotation values after approximately 12-16 weeks post-implant. However, when obtained from the cell culture of the invention described in Example 1 of the subject application, RCSN-3 cells reached a plateau significantly sooner, at approximately 6 weeks post-implant. The comparative data demonstrate that the cell culture of the invention is particularly advantageous for cell transplantation. The benefits of the claimed cell culture are unexpected in view of the prior art, and have a significant, practical advantage. Therefore, the applicants respectfully submit that the cell culture of the invention is not obvious over the cited references. Accordingly, in view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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